PATENT
PC10023A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: **J. TIMOTHY GREENAMYRE, et al.**

APPLICATION SERIAL NO.: **09/148,973** : Examiner: **K. MACMILLAN**

FILING DATE: **September 4, 1998** : Group Art Unit: **1618**

TITLE: **METHODS OF ADMINISTERING AN AMPA RECEPTOR ANTAGONIST TO TREAT DYSKINESIAS ASSOCIATED WITH DOPAMINE AGONIST THERAPY**

Assistant Commissioner for Patents
Washington, D.C. 20231

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231
ON THIS 27th DAY OF March 2000
BY Kristina L Konstus

COMMUNICATION IN RESPONSE TO SEPTEMBER 28, 1999 OFFICE ACTION

This Communication is being filed in response to the Office Action dated September 28, 1999 issued by the United States Patent and Trademark Office in connection with the above-identified application. A response to the September 28, 1999 Office Action was due three months therefrom, i.e. by December 28, 1999. Applicants are filing concurrently herewith a Petition for a three month extension of time for responding to the September 28, 1999 Office Action. With a three month extension of time, a response to the Office Action is not due until March 28, 2000, and this Communication is being timely filed.

Claims 1-8 are pending in this application. In the September 28, 1999 Office Action, claims 1-3 and 5-7 were rejected, and claim 4 and 8 were objected to. Reconsideration is respectfully requested in light of the following remarks.

The Examiner indicated that claims 4 and 8 are directed to allowable subject matter, but are objected to as being dependent from rejected claims.

The Examiner rejected claim 1-3 and 5-7 under 35 USC 103(a) as allegedly obvious over Arnold, et al., U.S. Patent 5,670,516. The Examiner stated that Arnold,

et al., teaches a method of treating neurological disorders by administering a compound that blocks or antagonizes AMPA receptors. According to the Examiner, claims 1-3 and 5-7 differ in that they are directed to treating a more specific neurological disorder, namely dyskinesia associated with dopamine agonist therapy. The Examiner stated that it would have been obvious to one of ordinary skill in the art to use AMPA antagonists to treat dyskinesia because Arnold, et al. allegedly teach that blocking AMPA receptors is an effective way to treat a variety of disorders, including dyskinesia. The Examiner cited claims 24 and 29 or Arnold, et al. The Examiner stated that one would have been motivated to do so with a reasonable expectation of success, because Arnold, et al., supposedly teaches dyskinesia as being among those neurological disorders responsive to AMPA antagonists. The Examiner stated that he acknowledged that Arnold, et al. exemplifies different AMPA antagonist compounds, but that claims 1-3 and 5-7 are not limited to any particular AMPA antagonists.

Applicants respectfully traverse the rejection over Arnold, et al. The present claims are directed to a method of treating dyskinesia associated with dopamine agonist therapy comprising administering an AMPA receptor antagonist. Applicants maintain that such method is not obvious from Arnold, et al. Arnold, et al. recites that excitatory amino acid (glutamic acid and aspartic acid) excitotoxicity has been implicated in the pathophysiology of acute and chronic neurodegenerative conditions (see column 1, lines 55-57). Arnold, et al., further recites that other neurological conditions, that are caused by glutamate dysfunction, ... include ... tardive dyskinesia (see column 1, line 66, through column 2, line 4). Arnold, et al. goes on to state that the use of a neuroprotective agent, such as an AMPA receptor antagonist, is believed to be useful in treating these disorders. Arnold, et al. does not state that patients afflicted with dyskinesias caused by dopamine agonist therapy, for example treatment with L-dopa or with a compound that agonizes dopamine receptors, can have their dyskinesias reduced from treatment with an AMPA receptor antagonist. Moreover, it is not seen how it would be obvious to use compounds indicated for treating dyskinesias associated with glutamate toxicity to treat dyskinesias associated with dopamine therapy. Accordingly, applicants respectfully request that the Examiner

reconsider and withdraw the aforementioned rejection of claims 1-3 and 5-7 under 35 USC 103 over Arnold, et al.

The Examiner also rejected claims 1-3 and 5-7 under 35 USC 103(a) as allegedly obvious over Klockgether, et al. The Examiner stated that the reference teaches that blocking AMPA receptors may provide a new strategy for treating Parkinson's disease. The Examiner stated that claims 1-3 and 5-7 differ in that they are drawn to treating dyskinesia associated with L-dopa therapy. The Examiner asserted, however, that it would have been obvious "to modify the process implied by Klockgether, et al." As motivation, the Examiner indicated that 1) Klockgether, et al. suggest treating PD patients who are on L-dopa therapy, as they suggest that AMPA antagonists can potentiate the actions of l-dopa, but reduce tremor associated therewith (citing page 18, column 2); and 2) Klockgether, et al.suggest dyskinesia, because Parkinson tremor is the main symptom of PD that results in dyskinesia.

Applicants traverse this rejection over Klockgether, et al. It is not found anywhere in Klockgether, et al., any statement that AMPA receptor antagonists reduce tremor associated with l-dopa. (Applicants are not sure exactly to which page the Examiner refers, since there is no page 18 of Klockgether, et al., only pages 717-723.) Moreover, Klockgether, et al. does not appear to even suggest that dyskinesias are a side effect of chronic l-dopa therapy. On page 720, second column, of Klockgether, et al., it is stated that NBQX (indicated in Klockgether, et al. to be a selective AMPA receptor antagonist) potentiates the actions of L-dopa and was not observed to produce apparent side effects (dyskinesias, vomiting, or psychological disturbance) at the doses tested. Thus, Klockgether, et al. was discussing side effects that might have been observed from the AMPA drug; Klockgether, et al. does not address any l-dopa side effects. Also, administering NBQX to a patient suffering dyskinesia from L-dopa therapy might actually be considered counterintuitive from Klockgether, et al., since one might expect NBQX to exacerbate the dyskinesia side effect of l-dopa, since Klockgether, et al. indicates that NBQX potentiates the effect of l-dopa. Thus, applicants maintain that the invention as recited in claims 1-8 of the present application is not obvious from Klockgether, et al., and applicants respectfully request that the Examiner reconsider and withdraw the rejection over Klockgether, et al.

The Examiner also rejected claims 1-3 and 5-7 under 35 USC 103(a) as allegedly obvious over Stella, et al. in view of Klockgether, et al., supra. The Examiner stated that Stella, et al. teaches administering glutamate antagonists to treat dyskinesias associated with l-dopa therapy in Parkinson's disease. The Examiner further stated that claims 1-3 and 5-7 differ because they recite administration of an AMPA receptor antagonist "as the glutamate antagonist". According to the Examiner, it would have been obvious to one of ordinary skill in the art to use AMPA antagonists as a glutamate antagonist, rather than "the NMDA antagonist". The Examiner asserted that one would have been motivated to make the substitution because Klockgether, et al. teach that both AMPA antagonists and NMDA antagonists are glutamate receptor antagonists, citing page 1, column 2, of Klockgether, et al.

Applicants traverse the aforementioned rejection over Stella, et al. in view of Klockgether, et al. Stella, et al. report findings alleged to suggest that NMDA receptor blockade may ameliorate the dyskinetic complications of long-term levodopa therapy. Stella, et al. state that "recent observations suggest that the motor response alterations induced by levo-dopa might reflect upregulation of certain glutamate receptor-mediated responses", and that "it is hardly surprising that drugs known to interact selectively with glutamatergic subsystems can influence motor function". Yet, despite these statements, the suggestions in Stella, et al. regarding dyskinesias from l-dopa treatment, are, however, limited to NMDA receptor antagonists. Stella, et al. does not suggest that any glutamate antagonist other than an NMDA antagonist can be used against dyskinesias induced by l-dopa treatment. Klockgether, et al. does not compensate for this deficiency, since Klockgether, et al. was published prior to Stella, et al. and thus merely demonstrates that AMPA receptor antagonists were available prior to the Stella, et al. reference. Thus, applicants maintain that Klockgether, et al. and Stella, et al. do not render the invention as recited in the subject claims obvious.

In conclusion, applicants maintain that claims 1-8 are directed to an unobvious inventions. Applicants respectfully request a favorable reply to this effect.

If a telephone interview would assist in the prosecution of the subject application, the Examiner is invited to telephone applicants' undersigned attorney at the telephone number provided.

No fee is believed necessary in connection with filing this Communication. However, if any fee is determined necessary in connection with filing this Communication, authorization is hereby given to charge such fee to Deposit Account No.16-1445.

Respectfully submitted,

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